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Cooperative Clinical Trial of Photodynamic Therapy With Photofrin II and Excimer Dye Laser for Early Gastric Cancer

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Background and Objective: **Photodynamic therapy (PDT) is a recently developed endoscopic method for treating malignant tumors. For obtaining more photodynamic action with less thermal effect, we employed as the excitation light source for PDT an excimer dye laser, which is a pulsed laser with extremely high peak power, instead of an argon dye laser, which is a continuous wave laser and has been used conventionally.**
Study Design/Materials and Methods: **The effect of PDT using Photofrin II and the excimer dye laser was evaluated in 27 patients with early gastric cancer.**
Results: **Complete responses (CR) were obtained in 88% of 24 assessable patients and the response rate was 100%. CR was observed in all cases of lesions of superficial depressed type without ulceration and/or with tumor diameter less than 2 cm. Regarding toxicity, mild cutaneous reaction and photosensitivity were seen and lasted several weeks. There were no serious abnormalities in laboratory tests.**
Conclusion: **We conclude that PDT is a promising modality for early gastric cancer.**

Key words: endoscopic treatment, PDT, porfimer sodium, pulsed laser

INTRODUCTION

Photodynamic therapy (PDT) is a recently developed endoscopic method for treating malignant tumors using hematoporphyrin derivative (HpD) as the photosensitizer and a laser as the excitation light source [1,2]. The principle of this method is to kill malignant cells by photo-chemical reaction rather than heat. Because HpD has a higher affinity for malignant tissue, when injected intravenously it is concentrated more and retained longer in malignant tissue than in normal tissue [3]. Thus by using weak laser light to

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irradiate the tumor region, malignant tissue can be destroyed selectively [4]. The active component of HpD is dihematoporphyrin ether/ester (DHE), and in recent years a more purified Photofrin II has been prepared by Dougherty and used for PDT.

In 1990, Mimura et al. [5] reported the results of PDT for early-stage gastric cancer using HpD and argon dye laser. Of the 31 cases with tumors less than 10 cm^2, 21 cases resulted in CR without recurrence (68%). The beam of the argon dye laser is a continuous wave, so the peak power of the beam increases the tissue penetrability decreases due to the thermal change of the treated tissue. On the other hand, pulsed excimer dye laser (EDL) has limited thermal effect, so high peak power of the beam can be achieved.

In 1990, therefore, we investigated an excimer dye laser as the excitation light source for PDT.

In this paper, we describe the results of our prospective cooperative trial in early gastric cancer with PDT using Photofrin II and the EDL, and discuss the indication for PDT.

MATERIALS AND METHODS

Eligibility Criteria

Eligibility criteria included 1) biopsy-proven early gastric cancer that was evaluated as mucosal or submucosal invasion, 2) either less than 3 cm in diameter or 7 cm^2 of tumor area, 3) entire tumor lesions visible endoscopically, 4) no prior therapy for targeted tumor lesion, 5) informed consent either of patients or their relatives before start of the therapy. There was no restriction on age of patients.

Photosensitizer

Photofrin II (PHE) is a purified hematoporphyrin derivative, and a freeze-dried cake or powder for intravenous use contains porfimer sodium 75 mg/vial. The active ingredient, porfimer sodium, consists of a mixture of porphyrin oligomers of up to eight porphyrin units. The main ingredient is dihematoporphyrin ether/ester. PHE was manufactured by American Cyanamid Co., New York, and was provided by Lederle (Japan) Co., Ltd.

Laser Equipment

The laser equipment employed in this trial was the excimer dye laser model PDT EDL-1 from Hamamatsu Photonics K.K. This laser system consists of an excimer laser which emits a pulsed laser beam coupled to a dye laser. Major specifications of this system are 1) laser wavelength: 630 nm; 2) pulse energy: maximum 8 mJ/pulse (with 0.8 mm quartz fiber), maximum 4 mJ/pulse (with 0.4 mm quartz fiber); 3) peak power: 800 kW (in 8 mJ/pulse), 400 kW (in 4 mJ/pulse); and 4) Pulse width: 10 nsec; pulse frequency: 20, 30, or 40 Hz [6].

PDT Procedure

Patients were intravenously given 2.0 mg/kg of PHE after 75 mg/vial of PHE dissolved with 30 ml of 5% glucose. Forty-eight to seventy-two hours later, the entire lesion plus about 5 mm width of marginal mucosa was irradiated with the EDL beam transmitted endoscopically. When the distance between the tumor surface and the fiber tip was 3.2 cm and the diversion angle of laser beam was 20°, the irradiation area was approximately 1 cm^2. The irradiation was delivered at a total dose of more than 60 J/cm^2. For wider lesions, the irradiation field was first set on the anal and posterior side of the lesion, and after delivering the scheduled dose of light there, the field of irradiation was shifted to the remaining part, so as to irradiate the entire region uniformly. Three hundred seventy-five seconds of irradiation were required to obtain 60 J/cm^2 with 4 mJ/pulse as maximum pulse energy, and 40 Hz as pulse frequency. Assuming that the irradiation was uniform, the total energy density (J/cm^2) of the irradiated area was calculated by the following formula: Total energy density (J/cm^2) = pulse energy(J/pulse) × pulse frequency(pulse/sec) × time(sec)/total irradiated area (cm^2). After PDT, the patients were given H_2-receptor antagonist for treating the sequential ulcer.

Evaluation of Response

By endoscopy with biopsy, the response to PDT was evaluated 1, 2, and 4 weeks, and 2, 3, and 6 months, and 1 year after PDT and every 6 months thereafter. Tumor response to treatment was evaluated as complete response (CR), no evidence of tumor both histologically and endoscopically for at least 4 weeks; partial response (PR), more than 50% reduction in size of tumor for at least four weeks; and no change (NC), no change in tumor.

Drugs other than PHE supposed to affect tumor response or adverse effects such as anticancer drugs were prohibited during PDT except for drugs for the treatment of adverse effects. For

safety, patients were exposed as little as possible to direct sunlight for at least 4 weeks after PDT, and were recommended to wear a wide-brimmed hat, sunglasses, sunscreen lotion, long-sleeved shirts, and gloves.

RESULTS

Patient Characteristics

Twenty-seven patients were entered between September 1990 and March 1992. Of these 27 patients, 24 were evaluable for response. Two ineligible patients had more than 7 cm^2 of tumor area. One inevaluable patient died of disease unrelated to the tumor treated before 4 weeks of CR duration.

The characteristics of the 25 eligible patients are summarized in Table 1. The median age was 72 years, and the median performance status (ECOG) was 0 just as the Karnofsky performance status was 100%. Five patients' tumor lesions were located in the upper third, ten in the middle third, and ten in the lower third of the stomach. Sixteen patients had well-differentiated adenocarcinoma, eight moderately differentiated adenocarcinoma, and one signet-ring cell carcinoma. Median tumor area was 2.0 cm^2. Seventeen had mucosal carcinomas and eight submucosal carcinomas. Four had superficial elevated type, nine superficial depressed type without ulceration, and twelve depressed type with ulceration of early gastric cancer.

Twenty-one patients were ineligible for conventional surgery, because of poor function of liver, lung, or kidney in 15 patients, and old age in 6. Six patients refused surgery.

Twenty-one of twenty-four patients resulted in CR (87.5%). Relapse occurred in three CR patients, two within 2.8 months, and one after 12.4 months. Three relapsed cases had such patient characteristics as submucosal invasion, more than 2.1 cm^2 tumor area, and more than 2 cm tumor size. Eighteen of twenty-one CR patients had no relapse between one and 15.3 months, with a median of 6.1 months. There are no particular patient characteristics which seem to influence the CR rate (Table 2), but patients with tumors less than 2 cm in diameter had higher CR rates than those with larger tumors.

TABLE 1. Characteristics for Eligible Cases

Sex	
Male	21
Female	4
Age	
50–59 (years)	2
60–69	6
70–79	14
80–89	2
90–	1
Performance status (EOCG)	
0	16
1	7
2	1
3	0
4	1
Tumor location	
Upper third	5
Middle third	10
Lower third	10
Histology	
Wel. dif. adenocarcinoma[a]	16
Mod. dif. adenocarcinoma[b]	8
Signet-ring cell carinoma	1
Tumor area	
–1.0 (cm^2)	11
1.1–2.0	2
2.1–4.0	8
4.1–7.0	4
Tumor size (diameter)	
< 2.0 (cm)	16
≥ 2.0	9
Depth of invasion	
Mucosal	17
Submucosal	8
Gross type	
Superficial elevated	4
Superficial depressed U1(−)[c]	9
Superficial depressed U1(+)[d]	12

[a]Well-differentiated adenocarcinoma.
[b]Moderately differentiated adenocarcinoma.
[c]Without ulceration.
[d]With ulceration.

Toxicity

Toxicity was evaluated in all 27 patients who entered the study. The results are summarized in Table 3. The main symptoms are skin reactions such as photosensitivity and the main abnormalities of laboratory tests are slight liver dysfunctions. Severe symptoms and abnormalities of laboratory tests due to PDT were not observed, except for 1 grade 3 anemia with decrease of hemoglobin to 6.2 g/dl.

Grade 3 anemia was caused by massive bleeding from an ulcer produced after PDT, and recovered only by conservative treatment such as blood transfusion, so endoscopic hemostasis was not carried out. All other toxicities were grade 1 or 2.

TABLE 2. Patient Characteristics and Response

Characteristics	CR	PR	Relapse in CR
Sex			
Male	18	2	3
Female	3	1	0
Age			
50–59 (years)	2	0	0
60–69	5	1	1
70–79	11	2	2
80–89	2	0	0
90–	1	0	0
Performance status (EOCG)			
0	14	2	1
1	6	1	1
2	1	0	1
Tumor location			
Upper third	3	1	1
Middle third	10	0	1
Lower third	8	2	1
Histology			
Wel. dif. adenocarcinoma[a]	13	2	2
Mod. dif. adenocarcinoma[b]	7	1	1
Signet-ring cell arcinoma	1	0	0
Tumor area			
–1.0 (cm^2)	10	0	0
1.1–2.0	1	1	0
2.1–4.0	7	1	1
4.1–7.0	3	1	2
Tumor size (diameter)			
< 2.0 (cm)	15	0	0
≥ 2.0	6	3	3
Depth of invasion			
Mucosal	14	2	0
Submucosal	7	1	3
Gross type			
Superficial elevated	3	1	0
Superficial depressed U1(−)[c]	8	0	1
Superficial depressed U1(+)[d]	10	2	2

[a]Well-differentiated adenocarcinoma.
[b]Moderately differentiated adenocarcinoma.
[c]Without ulceration.
[d]With ulceration.

TABLE 3. Side Effects

	Incidence (%)	Grade[a] 1	2	3	4
Flare	3 (11.1)	3			
Facial edema	1 (3.7)		1		
Photosensitivity	4 (14.8)	4			
Pigmentation	1 (3.7)	1			
Nausea	1 (3.7)	1			
Epigastric pain	1 (3.7)	1			
Gastric pain	1 (3.7)	1			
Erythrocyte ↓[b]	2 (7.4)				
Hemoglobin ↓	5 (18.5)	3	1	1	
Leucocyte ↑[b]	1 (3.7)				
Total protein[b]	2 (7.4)				
GOT ↑	4 (14.8)	3	1		
GPT ↑	3 (11.1)	2	1		
Al-p ↑	1 (3.7)	1			
γ-GTP ↑[b]	1 (3.7)				
BUN ↑	1 (3.7)	1			
Creatinine ↑	1 (3.7)	1			
Imbalanced K[b]	1 (3.7)				
Imbalanced Ca[b]	2 (7.4)				
Imbalanced Cl[b]	1 (3.7)				

[a]WHO grade.
[b]Not graded.

DISCUSSION

Efficacy of PDT Using Photofrin II and EDL

In 1990, Mimura et al. [5] reported the results of PDT for early-stage gastric cancer using HpD and argon dye laser. The rate of CR without recurrence by PDT was 59% (13/22) and 57% (8/14) for mucosal and submucosal carcinomas, respectively. Among the 31 lesions of less than 10 cm^2, the rate of CR without recurrence was 68% (13/19) and 67% (8/12) for mucosal and submucosal carcinomas, respectively. Our present data show that no recurrence of mucosal carcinoma was observed and the rate of CR without recurrence in PDT with EDL using Photofrin II is 88% (14/16) and 50% (4/8) for mucosal and submucosal carcinomas, respectively. Although these data cannot be compared directly with that of the above report, the effect of PDT for mucosal carcinomas is considered to be good. Okunaka et al. [7] reported that the tissue penetrability of EDL in the tumor-transplanted mice was 15 mm, so the EDL beam is considered to be able to penetrate the submucosal layer. The patient characteristics of recurrence cases were two with large tumor (6 cm^2, 7 cm^2) and one with the tumor located in the upper third of the stomach and difficult to irradiate endoscopically. The cause of recurrence was assumed to be insufficient irradiation. Especially for large tumors, uniform irradiation of the laser beam is difficult. The reasons for this difficulty are unevenness of irradiation and the loss of sight of the targeted tumor caused by white adventitious membrane and edema formed at the irradiated site and spasm of gastric wall. This is supported by our current data, which shows that the rate of CR is 100% (15/15) for lesions less than 2 cm in diameter and 67% (6/9) for lesions equal to or more than 2 cm. In the future, for PDT, more efficient irradiation using improved fibers will be necessary.

Clinical Use of PDT

The first line therapy for early gastric cancer is surgery. In recent years, early stage cases are

being detected as a result of improvements in survey and diagnostic techniques, and among them many patients are at high surgical risk due to coexisting hepatic, cardiovascular, or pulmonary disease. For these patients, endoscopic treatment is desirable. Several kinds of methods have been developed for the endoscopic treatment of early gastric cancer, such as strip biopsy, but none of them is very effective for treatment of the depressed type with ulceration. In this trial, in patients with superficial carcinoma with ulceration which was not indicated by other endoscopic treatment, the rate of CR reached 83% (10/12) using Photofrin II and EDL. This result is promising for the treatment of superficial carcinoma with ulceration. Therefore, the following conditions should be kept in mind when PDT is performed: 1) PDT is indicated in cases of superficial depressed carcinoma (including lesions with ulceration). The elevated type can be treated by other methods with less difficulty. 2) PDT is indicated for patients who are poor risks for surgery, because it is impossible to rule out lymph node metastasis at the cell level. 3) In patients with carcinoma 3 cm or less in diameter, CR without recurrence by PDT is expected. The rate of CR without recurrence is especially high in patients with carcinoma less than 2 cm in diameter.

Side Effects

Severe symptoms and abnormalities of laboratory tests were not observed, except for grade 3 anemia. Main toxicities were mild skin reactions such as photosensitivity and slight liver dysfunctions. Photofrin II tends to be retained in patients' cutaneous tissue after administration of this drug, and patients must be restricted from exposure to bright illumination or direct sunlight for at least 4 weeks.

REFERENCES

1. Dougherty TJ, Lawrence G, Kaufman JH, Boyle D, Weishaupt KR, Goldfarb A. Photoradiation in the treatment of recurrent breast carcinoma. J Natl Cancer Inst 1979; 62:231–237.
2. Hayata Y, Kato H, Konaka C, Ono J, Takizawa N. Hematoporphyrin derivative and laser photoradiation in the treatment of lung cancer. Chest 1982; 81:269–277.
3. Lipson RL, Baldes EJ. The photodynamic properties of a particular hematoporphyrin derivative. Arch Dermatol 1960; 82:508–516.
4. Mimura S, Ichi M, Okuda S. Clinical studies of HpD photodynamic therapy for early gastric cancer. In: Takemoto T, Kawai K, eds. "Recent Topics of Digestive Endoscopy." Amsterdam: Excerpta Medica, 1987, pp 113–120.
5. Mimura S, Ichii M, Imanishi K, Tatsuta M, Otani T, Okuda S. Evaluation of photodynamic therapy. Dig Endosc 1990; 2:265–274.
6. Hirano T, Suzuki K, Ishizuka M, Suzuki H, Miyaki S. Pulse laser application for PDT. Proceedings of the 11th Annual Meeting of the Japan Society for Laser Medicine 1990; 103–106 (in Japanese).
7. Okunaka T, Kato H, Konaka C, Sakai H, Kawabe H, Aisawa K. A comparison between argon-dye and eximer-dye laser for photodynamic effect in transplanted mouse tumor. Jpn J Cancer Res 1992; 83:226–231.